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Holt-Oram Syndrome: When hand deformity leads to diagnosis of congenital heart disease

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Abstract

Introduction: The following review paper is an in-depth analysis of a rare condition called Holt-Oram syndrome. It explores the underlying mechanisms of the condition's pathophysiology, its diverse clinical manifestations, symptoms, and the challenges associated with diagnosis and treatment.

Materials and methods: A thorough review of the extant literature was conducted using the PubMed and Google Scholar databases. The following keywords were used: „Holt-Oram Syndrome", „HOS", „TBX5 mutation", „Heart-Hand Syndrome", „congenital heart defect", „cardiac-limb syndrome"

Conclusions: Holt–Oram syndrome is a genetic disorder caused by mutations in the TBX5 gene, typically inherited in an autosomal dominant manner. However, de novo mutations have also been reported in some cases. A hallmark of this syndrome is upper limb malformation, most commonly affecting the radial ray. In approximately 70% of patients, congenital heart defects co-occur with limb abnormalities. The clinical spectrum of Holt–Oram syndrome is highly variable, ranging from mild anatomical changes to severe functional impairments. The diagnosis cannot be confirmed or ruled out using current diagnostic criteria, and confirmation requires molecular analysis of the TBX5 gene. This is because the picture may sometimes be incomplete, or the phenotype may overlap with other similar conditions. The management of Holt–Oram syndrome is highly individualized and closely tailored to the specific clinical manifestations present in each patient and also often requires the involvement of many specialists.

Keywords: „Holt-Oram Syndrome", „Heart-Hand Syndrome", „Thumb malformations", "TBX5 gene", "HOS"

Introduction

Holt-Oram syndrome is a unique genetic condition characterized by its autosomal dominant inheritance pattern. It is associated with a variety of disparate morphological and functional symptoms. The condition may manifest in several forms, including congenital heart disease and

anatomical deformities affecting the upper limbs. Furthermore, it is linked with specific genetic mutations in the TBX5 gene located on chromosome 12. The initial observation made in 1960 by M. Holt and S. Oram suggests the possibility of a genetic underpinning for the observed correlation between congenital heart deformities and hand malformations. The authors observed the presence of such symptoms across four generations within the same family (1,2). Recent technological advancements have enabled a more precise understanding of this syndrome. However, diagnosis can be challenging due to the complexity of the phenotypes involved.

Epidemiology

Several large clinical series of patients with Holt–Oram syndrome (HOS) have been published, primarily focusing on the clinical presentation, differential diagnosis, and diagnostic criteria. However, the number of population-based epidemiological studies remains limited due to the necessity of large sample sizes and standardized data collection. The estimated prevalence of HOS is approximately 0.95 per 100,000 births, based on a single epidemiological study performed in Hungary. The majority of clinical reports are focused on live-born (LB) children or adults, while there is a limited availability of data concerning fetal deaths (FD), terminations of pregnancy following prenatal ultrasound detection of severe anomalies (TOPFA), and cases diagnosed in the neonatal period (3). Current data suggests that it occurs with equal frequency across different racial and ethnic groups, and among both males and females (2,4,5).

Pathogenesis:

Holt-Oram syndrome is a condition that primarily affects the heart and upper limbs. The etiology of the disease is genetic, and its inheritance follows the patterns described by Mendel in autosomal dominant inheritance. However, in most cases, the mutation occurred de novo, without any prior family history of the disease (2,5,6). The association between Holt-Oram Syndrome, initially identified in 1960, and the TBX5 gene mutation was revealed in 1997 (7,8). Since that time, research has been conducted on the possible disease mechanism and the potential molecules involved (9). Two decades of progress in the field have led to a more comprehensive understanding of the pathogenesis of Holt-Oram Syndrome (10). The focal point of this research is the TBX5 gene, which is located on the long arm of chromosome 12q24.1 (11–14). It has been established that this gene is part of a larger family of transcription factors (15). Furthermore, mutations affecting other members of this family have been implicated in the pathogenesis of various conditions. For instance, TBX3 has been implicated

in ulnar-mammary syndrome (UMS), TBX4 has been assigned to "small nail patella" syndrome, and TBX1 has been linked to DiGeorge/ Velocardiofacial syndrome (4). TBX5 is also a component of the T-box family of transcription factors. Molecules belonging to this family have been shown to bind to DNA strands and act as transcription factors to regulate the expression of genes already relevant during early embryonic development. It is imperative to acknowledge the significance of this factor, as it plays a pivotal role in the formation of the heart septum, the establishment of the conduction system, and the development of the upper limb bones (7,15). At the onset of heart development, TBX5 is uniformly expressed in the heart; however, subsequently, its expression becomes restricted to the left side (7,16). Research has demonstrated that TBX5 is expressed during the developmental process in the free walls and septa of all cardiac chambers. In later stages, TBX5 is involved in differentiating and forming upper limb muscles and tendons (17). Current data and studies support the hypothesis that the underlying cause of Holt-Oram syndrome is primarily TBX5 haploinsufficiency (10). This condition indicates that a single correct copy of the gene is inadequate to ensure proper development of the areas controlled by this transcription factor (18). Mutations in the TBX5 gene have been identified in over 70% of individuals diagnosed with Holt–Oram syndrome. According to other authors, TBX5 mutations are identified in only about 30% of patients. These discrepancies are primarily due to variations in the diagnostic criteria for HOS and differences in the selection of patients for molecular testing (19). Pathogenic variants include missense and nonsense substitutions, large multi-exon deletions, frameshift mutations, and intragenic duplications (14,20). Furthermore, interactions with other transcription factors have been observed (20,21). TBX5 and NKX2 have been identified as being essential for the proper formation and function of the cardiovascular system, specifically concerning the ion channels involved in signal transduction (10). To enhance comprehension of the role of TBX5, researchers created a homozygote lacking both alleles. In a mouse model, this defect was found to be lethal. The embryos had serious developmental defects affecting the upper limbs and heart (10,22). Research has shown that Holt-Oram syndrome can present with various phenotypic variants, potentially due to incomplete penetrance of the causative mutation (12).

An analysis of the extant literature suggests a close correlation between the observed defects and the location of the mutation. When a missense mutation is present closer to the 5' end of the T-box5 gene, it has been observed that there is a greater probability of severe heart defects.

Similarly, the occurrence of a mutation in the immediate proximity to the 3' end, resulting in binding to the minor groove, has resulted in more extensive limb defects (19,23).

Symptoms:

This condition is characterized by congenital heart disease, skeletal malformations, primarily affecting the upper limbs, and conduction disturbances. The symptoms of Holt-Oram syndrome vary in severity, with patients ranging from those with asymptomatic findings to those presenting with severe, life-threatening conditions (24,25). A wide array of upper limb abnormalities has been documented in patient cases, including radial aplasia or hypoplasia, asymmetric arm lengths, dysfunctional forearm pronation and supination, restricted thumb mobility, downward-sloping shoulders, reduced shoulder range of motion, and complete lack of development of preaxial skeletal structures (11,13). Phocomelia can be observed as part of the limb abnormalities associated with the condition. The thumb may be completely absent, severely underdeveloped, or present as a triphalangeal structure. These deformities can occur on one or both sides of the body and can be symmetrical or asymmetrical. In the majority of cases, they are unilateral, most commonly affecting the left side of the body (6). Importantly, multiple upper limb deformities can coexist in a single patient. Another area affected by Holt-Oram syndrome is the heart. The most frequently reported cardiac anomalies include ostium secundum atrial septal defects, accounting for approximately 34% of cases, and ventricular septal defects, observed in about 25% (2,19,21). Other defects, such as patent ductus arteriosus, coarctation of the aorta with or without bicuspid aortic valve (BAV), mitral valve anomalies, left ventricular hypoplasia, and pulmonary stenosis, are also observed, though they are less prevalent than septal malformations (5,12,26). The severity of septal malformations can vary considerably, ranging from mild to life-threatening conditions. These defects may lead to serious complications, including pulmonary hypertension, congestive heart failure, and infective endocarditis (2). Holt-Oram syndrome is associated with an increased risk of cardiac conduction abnormalities. Early manifestations, such as sinus bradycardia or first-degree atrioventricular block, may be evident at birth, with potential progression to complete heart block occurring unpredictably. Additionally, arrhythmias, including atrial fibrillation and Wolff-Parkinson-White syndrome, have been reported in affected individuals (2,11,27). Cardiac conduction disorders can develop even in the absence of structural heart anomalies (3). In certain cases, features such as a pectus excavatum, pulmonary agenesis, and cardiomyopathies without septal defects have been observed (12). Clavicular hypoplasia and thoracic anomalies

may also be present (26,28). No clear correlation has been established between the severity of cardiac and limb malformations (3).

Diagnosis:

The diagnostic standards for Holt-Oram syndrome have been delineated. These include the presence of congenital heart defects or conduction disorders, in association with an anterior deformity in the radial part of at least one upper extremity. In the absence of cardiac anomalies, the presence of a family history of disease is indicative of its potential (3,20). Due to the genetic etiology of this condition, genetic testing may be a valid diagnostic modality in certain cases. Genetic testing is a valuable tool for identifying individuals who are at risk of this disease. This includes family members, such as parents and siblings, of individuals who have been diagnosed with HOS (13). This allows for the provision of effective cardiac treatment to patients who have not yet been diagnosed, thereby preventing sudden cardiac events (7,13). The diagnosis is uncomplicated in cases where all the relevant diagnostic criteria are met and a positive family medical history is present. The study also identified patients requiring differential diagnosis due to the presence of nonspecific symptoms (4). Conditions that can be confused with Holt-Oram syndrome include Okihiro syndrome, thrombocytopenia-absent radius (TAR) syndrome, Fanconi anemia, teratogen exposure (e.g., thalidomide, valproate), heart-hand syndrome type II (Tabatznik), heart-hand syndrome type III (Spanish type), Duane-radial ray syndrome, ulnar-mammary syndrome, long thumb brachydactyly, disorders associated with mutations in the SALL4 gene (such as Kaufmann-McKusick-Roberts or Nager syndrome), and VACTERL association (2,3,29). With thorough clinical evaluation, as well as cytogenetic and molecular testing, these conditions can usually be excluded (3). The diagnostic approach to a patient with suspected Holt-Oram syndrome (HOS) involves a comprehensive evaluation that includes physical examination, electrocardiography, cardiac catheterization, imaging studies such as X-rays and echocardiography, genetic testing, as well as assessment of family medical history (27). The physical examination focuses primarily on identifying visible deformities of the upper limbs. However, research has shown that in certain cases, these anomalies may be subtle or even imperceptible, with the only detectable abnormality being a delay in carpal bone maturation observed on wrist radiographs (20). For this reason, it is essential to obtain an anteroposterior X-ray of the wrist to detect such subtle skeletal findings (12,13). The diagnosis of Holt-Oram syndrome can be made prenatally. Between the 13th and 16th week of pregnancy, the radius and ulna become visible. Between the 18th and 20th week of pregnancy, the majority

of cardiac defects are identifiable. Research indicates that the timely identification of the syndrome during pregnancy allows for the strategic planning of the most suitable time and location for delivery, a matter of particular significance in cases of severe heart defects (6,19).

Treatment:

Treatment for Holt-Oram syndrome depends heavily on the individual's specific symptoms and overall clinical condition. Although upper limb anomalies significantly affect functional independence, it is the cardiac defects that carry the highest risk due to their potential to cause life-threatening events. For this reason, treatment must be tailored to each patient. Due to the possible complications of secondary congestive heart failure, pulmonary hypertension, arrhythmias, and sudden cardiac death, it is important to initiate therapy (27). Patients diagnosed with HOS frequently necessitate consultation with multiple medical specialists. These include medical genetics specialists, cardiologists, orthopedic surgeons, and plastic surgeons. Furthermore, the involvement of neonatologists is frequently crucial due to the congenital basis of the condition (13). There are no strict guidelines that define the approach to treating patients diagnosed with HOS. Accordingly, the extant literature describes procedures that focus on the control of individual symptoms (12,13). The spectrum of severity of mutations in the upper limbs is extensive, and as a result, some patients require corrective or reconstructive surgery to improve limb function. Physiotherapy and occupational therapy are frequently effective treatment options. However, the extant literature suggests that a significant number of patients with only subtle malformations do not receive any treatment in this regard. In the case of heart defects, treatment should be adapted to the patient's clinical condition. As Holt–Oram syndrome is present from birth, a significant proportion of patients require surgical correction of atrial septal defects (ASD) or ventricular septal defects (VSD) in early childhood. In patients who are not diagnosed until adulthood, the extant literature describes a variety of symptoms that prompt them to seek medical attention. In cases where a congenital heart defect leads to congestive heart failure, treatment may include diuretics, angiotensin-converting enzyme inhibitors, beta-blockers, or cardiac glycosides. Regular monitoring of the patient's condition is imperative. An annual electrocardiogram (ECG) is standard, while patients with conduction disorders are recommended to undergo annual 24-hour ECG monitoring (Holter). Another characteristic manifestation of Holt–Oram syndrome that may necessitate clinical intervention is cardiac arrhythmia resulting from conduction system abnormalities due to genetic mutations. Management in such cases may involve pharmacological therapy, surgical procedures, or

pacemaker implantation. Currently, there are no established guidelines regarding the optimal pacing strategy in patients with Holt–Oram syndrome. The literature describes a case of a patient with symptomatic bradycardia who underwent physiological His bundle pacing as an alternative to conventional right ventricular pacing. This approach was individually tailored to the patient's clinical profile and active lifestyle, to minimize the risk of pacing-induced heart failure (5). The most recent literature on the subject highlights the necessity of a specialized approach to patients with Holt–Oram syndrome in the context of perioperative management. It is imperative to consider the implementation of prophylactic antibiotic therapy not only in the context of complex surgical interventions, such as atrial or ventricular septal defect repair, but also in relation to less complex procedures, including tooth extractions. The purpose of this management is to prevent infectious complications, such as bacterial endocarditis or pericarditis (2). In addition, particular attention should be paid to a comprehensive assessment of the cardiovascular system. This is especially important given the rarity of the syndrome and the limited data available on potential perioperative risks. Patient with more severe forms of Holt-Oram syndrome may present with challenging vascular access, intraoperative arrhythmias, and hemodynamic instability. Moreover, due to the specific nature of the syndrome, the risk of cardiac arrest occurring during operation cannot be excluded. Furthermore, it has been observed that patients diagnosed with HOS appear to demonstrate an increased propensity for developing respiratory tract infections. Consequently, the extant state of knowledge supports the necessity of close monitoring of these patients and the implementation of lower thresholds for initiating antibiotic therapy (2).

Conclusions:

Holt-Oram syndrome is a rare condition that is inherited in an autosomal dominant pattern and it's associated with a mutation in the TBX5 gene. This highlights the importance of proper diagnosis for both patients and their relatives. A proper diagnosis enables family members who have not yet been diagnosed to receive care as well. This is important because it can prevent serious complications and improve patients' quality of life. Sometimes, an anomaly in the upper limb that seems insignificant may be the first sign of serious heart defects. However, diagnosing Holt–Oram syndrome is very challenging. The main difficulties include significant variation in clinical symptoms and their tendency to overlap with symptoms of other diseases. There is also a small patient population and limited availability of large clinical studies that could serve as a basis for developing clear diagnostic criteria. Treating patients with this syndrome is also

challenging. Treatment must be fully personalized and tailored to individual symptoms, requiring interdisciplinary cooperation between many specialists. For this reason, it is necessary to deepen our knowledge of this syndrome, not only in terms of diagnosis, but also pathogenesis and therapeutic options.

Disclosure

Author's contribution

Conceptualization: Dmowski Daniel, Adaśko Grzegorz

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